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Predicting the efficacy of surgery for pain relief in patients with alcoholic chronic pancreatitis

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ABSTRACT

Background: Recurrent pain is the most disabling complication in patients with chronic pancreatitis. Pancreatic surgery is currently considered as last-resort therapeutic option. The aims of this study were to assess pancreatic surgery performance for chronic pain in patients with alcoholic chronic pancreatitis and to determine factors predictive of therapeutic response.

Methods: All patients with chronic pancreatitis who underwent pancreatic surgery for chronic pain were included and divided into 2 groups according to the cause of chronic pancreatitis: alcoholic and any other chronic pancreatitis causes as the control group. Alcohol, tobacco, and painkiller intake, quality of life data 6 months and 1 year after surgery, and morphological and pathological features were analyzed.

Results: Fifty patients were included in the alcoholic chronic pancreatitis group and 16 patients in the control group. Smoking cessation before pancreatic surgery was achieved in 40% of the alcoholic chronic pancreatitis group compared with 73% of the control group ($P = .005$). Histological analysis revealed a higher prevalence of hypertrophic nerves and perineural inflammation in the alcoholic chronic pancreatitis group than in the control group ($P = .03$ and $P = .04$ respectively). In multivariate analysis, in the alcoholic chronic pancreatitis group, factors predictive of 6-month narcotic use cessation were surgery performed within a maximum of 2 years after chronic pancreatitis diagnosis (odds ratio = 4.228 [1.04–17.17]) and postoperative smoking cessation (odds ratio = 3.561 [1.021–12.41]); at 1 year, only smoking cessation was predictive of narcotic use cessation (odds ratio = 11.33 [2.677–47.98]).

Conclusion: In patients with alcoholic chronic pancreatitis undergoing surgery for chronic pain, narcotic use cessation and improved quality of life depend on early surgery and complete smoking cessation.

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Nearly 90% of patients with chronic pancreatitis (CP) report disabling pancreatic pain, which is the main cause of hospitalization.[1] Pain can lead to weight loss, depressive syndrome, addiction to painkillers or drug misuse, as well as impairment of quality of life.[2] A permanent pain characteristic seems to have a more deleterious impact on quality of life than the intensity of the pain itself.[3]

Several studies highlighted great variability regarding the duration of pain evolution during CP natural history and a lack of correlation with its intensity.[3,4] After a median follow-up of 11 years, fewer than 1 in 2 patients (47%) reported a decrease in pancreatic pain over the CP course.[5]

Chronic pain genesis has long been reduced to a pure mechanistic theory, related to hyperpressure caused by pancreatic duct obstruction. It is now well known that pain genesis is multimodal, which explains some therapeutic failures when the choice of treatment is based only on morphological abnormalities. The main components inducing chronic pain are pancreatic and extrapancreatic visceral nociceptive neuronal activation, peripheral and central neurological impairments, and peri-pancreatic complications such as pseudocysts.[6]

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Neuronal plasticity corresponding to the increase in number and size of nerves within the pancreas was described.[7] After peripheral nerve lesions, central neurological sensitization, at both the medullary and cortical levels, might maintain pain.[4,8,9]

The therapeutic strategy commonly applied is a step-up approach, which combines dietary restrictions, focused mainly on ending exposure to risk factors (alcohol and tobacco), with an optimized analgesic medical treatment.[9] Medical treatment can combine analgesics of the 3 levels of the WHO classification with adjuvant treatments such as pregabalin and antioxidants. Pregabalin represents a key treatment for chronic pain because of its neurological action, both central and peripheral. Randomized trials highlighted significant improvements in pain rating scales (ie, Izbicki score) and a morphine sparing effect related to the use of pregabalin (compared with placebo), after only 3 weeks.[10,11]

Oxidative stress is known to be implicated in the pathogenesis of chronic pancreatitis. Among adjuvant therapies, antioxidants have been studied through randomized trials and appear to have a benefit in pain reduction for patients with chronic pancreatitis.[12-14] In a meta-analysis, Rustagi et al.[12] found that patients who received antioxidant therapy had significant reductions in the number of painful days per month and in the number of analagesics consumed per month.

Pancreatic surgery currently appears to be the last resort of the therapeutic strategy, especially after endoscopic treatment failure.

There are no clear predictive markers for the evolution of chronic pain or the response to different treatments during CP. Only one study identified 3 risk factors for surgical treatment failure: long-term morphine intake, prolonged chronic pain, and a history of more than 5 endoscopic treatments.[15]

The main objective of this study was to evaluate the efficacy of analgesic pancreatic surgery in patients with alcoholic CP and to determine the clinical, morphological, and histological factors predictive of the therapeutic response.

Methods

Patients

A retrospective monocentric study was performed at Beaujon Hospital (France). All files of patients with CP who underwent pancreatic surgery, regardless of the indication, were analyzed to determine their eligibility. All patients monitored for CP and operated on for recurrent pain between 2008 and 2015 were included.

Inclusion criteria

1. Two groups were studied and compared: The first group comprised patients with alcoholic CP. The second group, the control group, comprised patients with non-alcoholic CP. The causes of CP were genetic (mutations of the PRSS1, CFTR, CTRC, or SPINK1 gene), autoimmune (pathological confirmation), or idiopathic after an exhaustive workup.
2. All patients presented with chronic or recurrent acute bouts of pain, and pancreatic surgery was carried out with the intent of relieving pain in all cases. Surgical procedures included pancreatic resections and drainages. Resections included the Frey and Whipple procedures and left (LP) and median (MP) pancreatectomies. The drainage surgery consisted of a longitudinal opening of the main pancreatic duct (MPD) with Wirsungo-jejunal anastomosis.
3. All patients included had a preoperative pancreatic computed tomographyscan.
4. All surgical specimens were available in the Department of Pathology.

Exclusion criteria

1. Patients with suspected pancreatic tumors or in whom pancreatic cancer was diagnosed within 1year following surgery were excluded.
2. In the control group, all patients with chronic alcoholic consumption above World Health Organization (WHO) recommendations were excluded (>30 g/day for men, >20 g/day for women).

Definitions

Chronic pancreatitis diagnosis was based on a set of clinical and morphological data, with histological confirmation for all patients.

The alcoholic origin of the CP was defined as consumption of >80 g/day alcohol during and more than 10 years.[16] Exocrine pancreatic insufficiency (EPI) was defined by the existence of steatorrhea, need for oral pancreatic enzyme supplementation, or a fecal elastase-1 <100 µg/g stool.

Consumption of analgesics was reported according to the levels set by WHO (1–3) and the mean daily dose. A specific conversion for each analgesic was performed so that all results would be expressed as oral morphine equivalents (OMEs) corresponding to the dose of morphine sulfate taken per day (see Supplementary Data, Appendix 1).

We assessed quality of life with objective data for all patients including analgesic use (1 to 3 levels set by WHO and mean daily dose), pain frequency (daily, weekly, monthly), and weight. All these data were part of our flowchart consultation procedures and were systematically reported in a standardized manner. The quality of life of the patient was rated as good (absence of pain or fewer than one pain episode per week and a normal food intake), average (weekly pain requiring analgesics and/or restriction of diet without sickness), or poor (daily pain requiring daily intake of analgesics and/or a restriction of diet responsible for weight loss).

Radiological analysis

All included patients had a preoperative abdominal CT scan. A senior radiologist expert in the pancreatic field, blinded to clinical and pathological findings, reviewed all exams.

Pathological analysis

All slides were reviewed by 3 authors (B.B., A.C., and V.R.), blinded to the clinical and radiological results. For each patient, all archived HES (hematoxylin-eosin-safran)-stained slides, representative of the entire surgical specimen, were analyzed.

All immunohistochemical techniques were carried out on the same automaton (Nexes GX, Ventana, Tucson, AZ, USA) within the Department of Pathology at Beaujon Hospital. The immunolabeling was carried out after selection of the most representative block from analysis of the HES-colored slides. Sections of 4 µm were made in the tissue blocks included in paraffin. The slides were immunolabeled with monoclonal antibodies against CD56 (clone 1B6, dilution 1/50, Leica Biosystems [formerly Novocastra], Nussloch, Germany); CD8 (clone C8/144B, dilution 1/50, DAKO, Carpinteria, CA) and tryptase (dilution 1/1000, Leica Biosystems). The paraffin sections were immunolabeled after dewaxing and rehydration of the slides. Antigen unmasking was performed following pretreatment at high temperature. Substitution of the primary antibody with phosphate-buffered saline was used as a negative control. The positive controls consisted of cellular elements always stained by the antibodies used: normal nerves for CD56, lymphocytes for CD8, mast cells for tryptase. After staining, the slides were scanned using a computer-controlled image capture device (Aperio, Leica

Biosystems, Nanterre, France) for morphometric analysis. A manual selection by contouring of one or more representative zones was made on the scanned slides, which were analyzed using the PRECISION image processing software (Aperio) to quantify the staining with the antibodies tested.

Data collection

The clinical characteristics recorded for each patient were age at surgery; sex; preoperative smoker status and tobacco consumption; alcohol cessation; pre- and postoperative diabetes mellitus; pre- and postoperative EPI; previous endoscopic treatment; analgesic use before surgery and 6 months and 1 year after surgery; quality of life at 6 months and 1 year after surgery; antidepressant therapy; type of pancreatic surgery; and delay between CP diagnosis and surgery.

Radiological criteria of interest are provided in the Supplementary Data, Appendix 2.

Histology

For each patient, the HES slides were counted and the total area of tissue analyzed on all HES slides was calculated (in mm^2). The histological criteria studied were classified into two categories: nerves and fibrosis.

For *nerves*, the criteria studied were (1) the morphology (dysmorphic and/or hypertrophic aspect) and (2) the presence of perineural inflammation. A semiquantitative score was established for each histological criterion and rated from 0 to 3. For the study of pancreatic nerves, 0 = absence of nerve lesions, 1 = <10% of the nerves with pathological lesions, 2 = 10%–50% of the nerves showing pathological lesions, 3 = >50% of the nerves showing pathological lesions.

For *fibrosis*, the criteria studied were (1) loss of islets of Langerhans (scored yes or no); (2) loss of acinus (scored 0 to 3); (3) presence of lymphocytic inflammation (scored 0 to 3); and (4) presence of abscesses (scored yes or no and numbered). The semiquantitative score used for criteria 2 and 3 was 0 = absence, 1 = <10%, 2 = 10%–50%, 3 = >50%.

Immunohistochemistry

The density of the inflammatory lymphocytic and mast cell infiltrates was studied after labeling with CD8 and tryptase antibodies, respectively. Nerve density was evaluated after labeling with the monoclonal antibody to CD56. For each of these markers, the immunolabeled area was calculated and related to the total area of the slide studied. Moreover, for CD56, the outbreaks comprising (1) loss of delineation of the perineurium, (2) thickening of the perineum, and (3) enlargement of the endoneurium were counted for each patient.

Statistical analyses

General characteristics were expressed as median and ranges or percentages. General characteristics and clinical, morphological, and histological data were compared using the Kruskall–Wallis test for continuous data and the exact Fisher or χ^2 test for qualitative data. A Spearman correlation coefficient was used to find an association between continuous variables. A multivariate analysis was carried out by logistic regression to search for risk factors of unresponsiveness to surgery performed with an analgesic aim. *P* values < 0.20 were considered significant as entry level in the model. Data were analyzed using SAS 9.1 software (SAS Institute Inc., Cary, NC). All statistical tests performed were two-sided.

Results

General characteristics of patients

General characteristics are summarized in Table I.

Fifty patients were included in the alcoholic CP group and 16 patients in the control group. The sex ratio was 7/1 (88% men) in the alcoholic CP group and 1/1 in the control group ($P < .001$). Age at surgery was similar in the 2 groups, 47 (32–64) and 54 (33–78) years ($P = .13$). One hundred percent of the patients were smokers before surgery in the alcoholic CP group compared with 69% in the control group ($P < .0001$). The median tobacco intake was 30 (10–90) and 17 (5–44) pack-years. The preoperative smoking cessation in the alcoholic CP group and control group was 40% and 73% ($P = .005$), respectively. Preoperative alcohol cessation in the alcoholic CP group was 80%.

The delay between CP diagnosis and pancreatic surgery was similar for the 2 populations: 4.67 (0.83–22.5) and 5.09 (2.18–17.6) years ($P = .56$). Before surgery, diabetes and EPI were more frequent in alcoholic patients (36% and 58%) than in controls (respectively, 6% $P = .02$ and 31% $P = .03$).

The type of surgery was similar for both groups.

Univariate analysis

Data on morphine consumption and quality of life are summarized in Table II.

Narcotic use cessation was attained at 6 months and 1 year in 46% and 54% of the alcoholic group and 94% of the control group ($P < .01$).

The quality of life at 6 months was good in 26 (52%), average in 17 (34%), and poor in 7 alcoholic CP patients (14%). In the control group, QOL was good in 15 (94%), average in 1 (6%), and poor in none $P = .0061$). One year after surgery, quality of life was good in 27 (54%), average in 12 (24%), and poor in 11 (22%) patients in the alcoholic CP group compared with the control group for which the distribution was the same as at 6 months ($P = .01$).

In both groups, narcotic use cessation at 6 months or 1 year was associated with a better quality of life ($P < .001$ for the alcoholic CP group, $P = .06$ for the control group).

In alcoholics, a short delay (≤2 years) between CP diagnosis and surgery was associated with narcotic use cessation at 6 months ($r = 0.35$, $P = .01$) and at 1 year ($r = .24$, $P = .08$) postoperatively.

There were no statistical differences between type of surgery (resection or drainage) and morphine weaning or quality of life, in both groups.

In patients with alcoholic CP, smoking cessation was associated with narcotic use cessation at 6 months ($P = .027$) and at 1 year ($P < .001$), alcohol cessation ($P = .003$), and good quality of life at 6 months ($P = .03$) and 1 year ($P = .012$).

Multivariate analysis

In the alcoholic CP group, morphine weaning at 6 months was associated with surgery within a <2-year period after CP diagnosis (odds ratio [OR] = 4.23 [1.04–17.17]) and smoking cessation (OR = 3.56 [1.021–12.41]). At 1 year, morphine weaning was only associated with smoking cessation (OR = 11.33 [2.68–47.98]).

Radiological characteristics

All morphological features are listed in Table III.

Pancreatic calcifications were found on preoperative imaging in 45 patients (92%) in the alcoholic group and 14 controls (87%). Their locations were similar in both groups (Fig. 1).

Table I
Patients' characteristics.

Characteristic	Alcoholic CP($N=50$)	Non-alcoholic CP($N=16$)	P
Age at surgery (y)	47 (32–64)	54 (33–78)	.13
Sex			
Men	44 (88%)	9 (56%)	
Women	6 (12%)	7 (44%)	
Smoking	50 (100%)	11 (69%)	<.0001
Tobacco intake (pack-years)	30 (10–90)	17 (5–44)	
Preoperative alcohol withdrawal	40 (80%)	15 (94%)	.27
Preoperative smoking cessation	20 (40%)	8 (73%)	.005
Time between diagnosis of CP and surgery (y)	4.67 (0.83–22.5)	5.09 (2.18–17.6)	.38
Surgical procedure			
Resection	45 (90%)	14 (88%)	
Whipple procedure*	6 (12%)	3 (19%)	
Frey procedure†	35 (70%)	7 (44%)	
Left pancreatectomy	4 (8%)	2 (12%)	
Median pancreatectomy	0	2 (12%)	
Drainage	5 (10%)	2 (12%)	
Diabetes			
Before surgery	18 (36%)	1 (6%)	.02
After surgery	24 (48%)	7 (44%)	1
Exocrine pancreatic insufficiency			
Before surgery	29 (58%)	5 (31%)	.03
After surgery	37 (74%)	12 (75%)	.94
Prior endoscopic treatment	15 (30%)	4 (25%)	1
Efficiency	9 (60%)	2 (50%)	1
Antidepressant medication	15 (30%)	1 (6%)	.03
Total	$N=50$	$N=16$	$N=66$

* Cephalic pancreaticoduodenectomy.
† Recess of the pancreatic head associated with a Wirsungo-jejunal anastomosis.
CP, chronic pancreatitis; *NS,* nonsignificant.

Table II
Morphine consumption and quality of life.

Parameter	Alcoholic CP($N=50$)	Non-alcoholic CP($N=16$)	P
Morphine consumption (OMEs)			
Before surgery (mg)	60 (20–500)	30 (20–120)	
After surgery at 6 months (mg)	20 (0–360)	0 (0–20)	
After surgery at 1 year (mg)	0 (0–360)	0 (0–20)	
Morphine sparing effect			
At 6 mo	37 (74%)	16 (100%)	
At 1 y		16 (100%)	
Morphine withdrawal			
At 6 mo	23 (46%)	15 (94%)	<.001
At 1 y	27 (54%)	15 (94%)	<.01
Quality of life[a] before surgery			
Good	0	0	
Average	0	0	
Poor	50 (100%)	16 (100%)	
Quality of life[a] 6 mo after surgery			.0061
Good	26 (52%)	15 (94%)	
Average	17 (34%)	1 (6%)	
Poor	7 (14%)	0	
Quality of life[a] 1 y after surgery			.01
Good	27 (54%)	15 (94%)	
Average	12 (24%)	1 (6%)	
Poor	11 (22%)	0	
Total	$N=50$	$N=16$	$N=66$

[a] Good = absence of pain or less than one pain episode/week and normal food intake; average = weekly pain requiring analgesics and/or restriction of diet with stable weight; Poor = daily pain requiring a daily intake of analgesics and/or a restriction of diet responsible for weight loss.
CP, chronic pancreatitis; *OMEs,* oral morphine equivalents (mg/day).

We looked for an association between pain and specific locations of inflammation. Thus, we assessed intrapancreatic, peripancreatic, celiac, and hepatic pedicle inflammation. We also especially analyzed inflammatory changes of the fat tissue localized in the posterior plane of the entire pancreatic gland. This so-called "pancreatic posterior surface inflammation" was statistically more frequent in alcoholic CP group patients (53%) than in controls (25%) ($P=.05$). Finally, left-sided portal hypertension, defined as a localized venous collateral formation caused by localized obstruction of the splenic vein, was assessed. This "segmental portal hypertension" was more frequent in the alcoholic group (69% vs 31%, $P=.0069$).

Pathological characteristics

Pathological characteristics are reported in Table IV. Nerve abnormalities are compared in Fig. 2 (*a*, *b*). In the alcoholic group,

Table III
Morphological characteristics (preoperative CT scan).

Characteristic	Alcoholic CP($N=42$)	Non-alcoholic CP($N=14$)	P
Calcifications	46 (92%)	14 (87%)	.62
Location			
Head	44 (88%)	12 (75%)	.23
Body	37 (75%)	11 (69%)	.75
Tail	29 (59%)	9 (56%)	1
Size of largest calcification (mm)	12 (3–23)	15 (3–20)	.29
Size of pancreas (mm)			
Head	40 (20–70)	33 (4–46)	.0069
Body	20 (10–45)	18 (12–30)	.41
Tail	18 (10–77)	17 (10–24)	.35
Size of main pancreatic duct (mm)			
Head	8 (1–16)	6 (1–17)	.065
Body	8 (2–19)	7 (1–12)	.48
Tail	5 (1–13)	5 (1–10)	.73
Main pancreatic duct stenosis	42 (86%)	12 (75%)	.46
Size of common bile duct (mm)	10 (3–20)	7 (3–15)	.066
Inflammation			
Intrapancreatic	32 (65%)	8 (50%)	.38
Peripancreatic	38 (77%)	11 (69%)	.74
Posterior surface	26 (53%)	4 (25%)	0.05
Celiac	10 (20%)	3 (19%)	1
Hepatic pedicle	26 (53%)	9 (56%)	.84
Pseudocyst	19 (39%)	4 (25%)	.38
Cystic dystrophy in heterotopic pancreas	9 (18%)	4 (25%)	.72
Venous thrombosis	15 (30%)	4(25%)	1
Segmental portal hypertension	34 (69%)	5 (31%)	.0069
Lymphadenopathy	24 (49%)	8 (50%)	.92
Total	$N=50$	$N=16$	$N=66$

CP, chronic pancreatitis; *NS,* nonsignificant.

Table IV
Pathological characteristics.

Characteristic	Alcoholic CP($N=42$)	Non-alcoholic CP($N=14$)	P
Overall surface area studied (mm)	1887 (250–8075)	1537 (425–4000)	NS
Dysmorphic and hypertrophic nerves*			.03
0	1 (3%)	4 (28%)	
1	11 (26%)	2 (14%)	
2	11 (26%)	4 (28%)	
3	19 (45%)	4 (28%)	
Perineural inflammation*			.04
0	5 (12%)	7 (50%)	
1	11 (26%)	2 (14%)	
2	14 (34%)	3 (21%)	
3	12 (29%)	2 (14%)	
Acute inflammatory foci	0 (0–3)	2 (0–4)	NS
Loss of acini*			
0	9 (21%)	1 (7%)	NS
1	13 (31%)	6 (43%)	NS
2	13 (31%)	2 (14%)	NS
3	7 (16%)	5 (36%)	NS
Lymphocytic infiltrate within fibrosis*			
0	23 (55%)	7 (50%)	NS
1	9 (21%)	1 (7%)	NS
2	10 (24%)	6 (43%)	NS
3	0	0	NS
Total	$N=42$	$N=14$	$N=56$

* A semiquantitative score was used for evaluation of these criteria: 0 = absence of lesion, 1 = <10%, 2 = 10%–50%, 3 = >50%.
CP, chronic pancreatitis; *NS,* nonsignificant.

the score quantifying the dysmorphic and hypertrophic nerves was 0, 1, 2, and 3 in 3%, 26%, 26%, and 45% of patients, respectively. In the control group, this score was 0, 1, 2, and 3 in respectively 28%, 14%, 28%, and 28% ($P=.03$). The scores for perineural inflammation were 1 in 5 (12%), 2 in 11 (26%), 3 in 14 (34%), and 4 in 12 (29%) alcoholic CP patients and 7 (50%), 2 (14%), 3 (21%), and 2 (14%) controls, respectively ($P=.04$). Lymphocytic inflammatory infiltrates and dysmorphic and hypertrophic appearance of the pancreatic nerves were more intense in patients with alcoholic CP (Fig. 1).

On immunohistochemistry, a high quantification score for CD56+ dysmorphic and hypertrophic nerves was associated with a higher density of CD8+ lymphocytic infiltrate ($P=.08$), but not with mast cell density. A high score for perineural inflam-

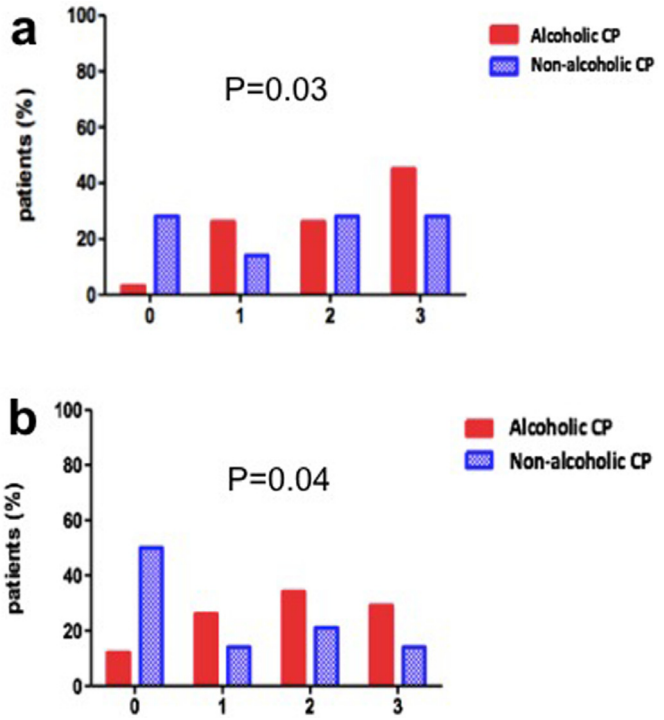

Fig. 1. Pathological analysis: (a–c) Immunohistochemistry with CD56 staining; (d–f) Hematoxylin–eosin stain. Inflammatory cell infiltrate and pancreatic nerve abnormalities on histological sections from a patient with alcoholic chronic pancreatitis. (*) Dysmorphic and hypertrophic nerves; (⋆) perineural inflammation.

mation was associated with high-intensity CD56 immunolabeling ($P = .056$). A high CD8 lymphocytic infiltrate was significantly associated with a larger number of foci of CD56-positive "pancreatic neuropathy" ($r = .33$, $P = .038$).

Morphine weaning at 1 year was associated with a lower density of infiltrating tryptase-positive mast cells in the patients concerned ($P = .09$). The number of CD56+ nerve foci was higher in the alcoholic CP group ($P = .07$). There was no statistical difference between the 2 groups with respect to the immunostaining of inflammatory lymphocytic or mast cells.

Discussion

After pancreatic surgery for chronic pain, weaning from morphine at 6 months or 1 year was markedly lower in patients with alcoholic CP (50%) than in patients with non-alcohol-related CP, almost all of whom (94%) no longer consumed opiates. A similar result was obtained with respect to quality of life. Unlike patients with alcoholic CP, for whom the benefit of surgical treatment appeared to be related to the duration of evolution of the CP, the efficacy of the treatment was the same regardless of the delay between diagnosis and surgery for patients with CP of other origins. In multivariate analysis, the main factor related to the success of the surgery for an effective long-term narcotic use cessation and a better quality of life was smoking cessation (OR = 11,33 [2.68–47.98]).

Tobacco has long been reduced to a cofactor of risk in the occurrence of CP, in association with chronic alcoholism.[17–19] Many studies have since demonstrated the independent role of tobacco as a risk factor for CP.[20,21] In a recent meta-analysis, the risk of CP for active smokers was estimated to be 2.8 (1.8–4.2) and 2.5 (1.3–4.6) after adjustment for alcohol consumption. A dose effect was observed: the relative risk of CP was 2.4 (0.9–6.6) and 3.3 (1.4–7.9) for the consumption of <1 and ≥ 1 pack/day. Smoking accelerates the progression of CP and increases the mortality rate during CP.[22] In an animal study, activation of pancreatic stellate cells by cigarette substances (tobacco smoke extracts and acetone nitrosamide derived from nicotine), in association (or not) with alcohol intake, was observed. These cells, whose role in the development of CP is known, express nicotinic receptors to acetylcholine.[23] Tobacco cessation should be a major concern, even though it is probably the hardest challenge, as only 40% of patients in the alcoholic CP group were weaned before surgery.[24]

This study is the first to compare the effectiveness of surgical treatment, according to the etiology of CP, with analysis of clinical, morphological, and histological data. In the alcoholic CP group, histological analysis revealed a higher prevalence of hypertrophic and dysmorphic nerves, as well as a greater lymphocytic inflammatory perineural infiltrate.

Even though it is difficult to provide a clear pathophysiological explanation for this difference, it is possible to evoke the pro-inflammatory role of tobacco. Its toxicity to the pancreatic parenchyma has clearly been demonstrated in animal models after chronic inhalation. In two studies, Wittel et al.[25,26] reported an inflammatory process associated with two distinct morphological

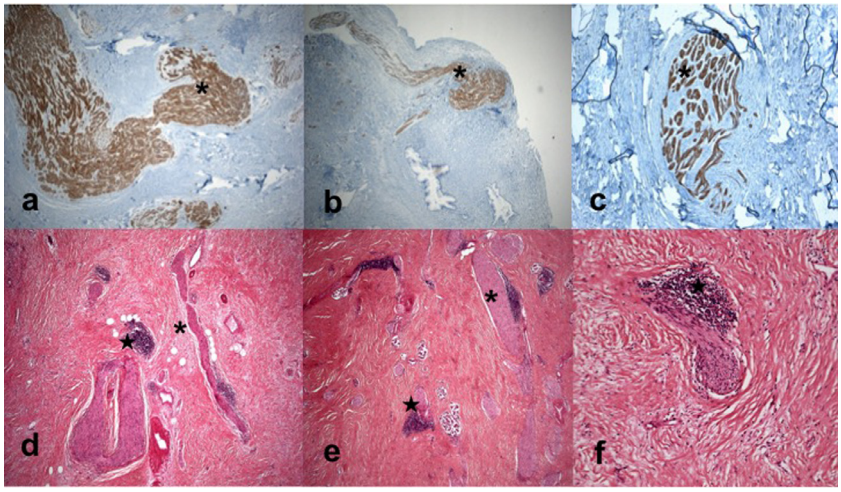

Fig. 2. Dysmorphic and hypertrophic nerves (a) and perineural inflammation (b) semiquantitative pathological scores in patients with alcoholic and nonalcoholic chronic pancreatitis (CP).

types of pancreatic lesions: an increase in extracellular matrix synthesis and a decrease in acinar structures in the lobular architecture, associated with infiltration by inflammatory cells.

Immunohistochemical analysis of the composition of the inflammatory infiltrate in our study revealed the association between low mast cell density and 1-year morphine weaning. Demir et al.[27] reported similar data within their cohort, in which the proportion of mast cells was higher in patients describing pain than in patients not feeling pain.

The superiority of surgery compared with endoscopic treatment in the control of chronic pain during CP has already been described.[28,29] In our study, a small proportion of patients in both groups (25%–30%) underwent endoscopic treatment prior to surgery, mainly because a large proportion of patients presented with pancreatic head enlargement and/or poorly dilated MPD and, to a lesser extent, a "center-dependent" effect. Endoscopic treatment also makes it possible to select future "good candidates" for surgery. Indeed, Kwon et al.[30] recently reported, in a retrospective study, that narcotic use cessation after the endoscopic implantation of a pancreatic stent was strongly associated with postoperative morphine weaning (OR = 38. $P = .0025$).

Our study confirmed the value of early surgery during CP to achieve a more important and lasting effect on pain control as described in other studies. Ahmed et al.,[15] in a cohort comprising 266 patients with CP, operated with the aim of analgesia and with a median follow-up of 62 months; they found that surgery performed within 3 years of the onset of pancreatic pain was associated with a greater decrease in the latter (OR = 1.8, 95% confidence interval: 1–3.4, $P = .03$). The disappearance of pancreatic pain in this study ranged from 23% to 75% depending on the use of preoperative morphine analgesics and the number of attempts at previous endoscopic treatment (≤ 5 or >5).

In conclusion, the therapeutic step-up strategy is increasingly discussed and balanced with an inverse top-down approach in which invasive treatments and especially surgery are initiated at an earlier stage in the development of CP. As currently recommended by experts, analgesic therapies during CP should be integrated into a therapeutic strategy individualized for each patient, taking into account the cause of the CP. This strategy must be determined as a multidisciplinary process, systematically including the advice of a pain specialist, given the multimodal nature and complex pathophysiology of this chronic pain. Surgery is probably less effective in alcoholic CP than in CP of other etiology, as illustrated in this study. The indication of surgery as a treatment for pain should be proposed to patients weaned from alcohol and especially from tobacco.

Conflict of interest disclosure

No conflicts of interest exist.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.05.025.

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